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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/272,809	03/19/1999	JOHN CLARK LAGARIAS	UCDVP009/99-219-1	6118

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/272,809	LAGARIAS, JOHN CLARK	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,8,10-19 and 22-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,8,10-19 and 22-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The amendment filed December 28, 2007 has been entered. The amendments to the specification have been entered. Claims 1, 8 and 17 have been amended. Claims 2, 6, 9 and 20-21 have been cancelled. Claims 1, 3-5, 7, 8, 10-19 and 22-32 are under consideration in this office action.

Priority

2. This application is claiming the benefit of prior-filed nonprovisional application No. 08/904,871, now issued as US Patent 6,046,014 under 35 U.S.C. 120 is granted.

Withdrawal of Objections and Rejections

3. The following objections and rejections have been withdrawn in view of applicants' amendments and arguments:

a) The objection to the specification under 35 U.S.C. 132(a) because it introduces new matter into the disclosure;

b) The rejection of claims 1, 3, 7, 9-19, 22, 25 and 27-32 under 35 U.S.C. 102(b) as being anticipated by Lagarias et al., WO 98/05944 (published 12 February 1998); and

c) The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Marshall and Neale submitted to the EMBL Data Library March 1995.

Response to Arguments

4. Applicant's arguments with respect to claims 1, 3-5, 7, 8, 10-19 and 22-32 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Objection

Claim Objections

5. Claims 10-16 are objected to because of the following informalities: Claims 10-16 are dependant upon cancelled claim 9. Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 3, 10, 17-19, 22 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Hill et al., (Eur. J. Biochem. 1994. Vol. 223:69-77)

Claim 1 is drawn to a composition comprising: an apophytochrome polypeptide consisting of less than about 400 amino acids, which apophytochrome polypeptide comprises a lyase domain having lyase activity, wherein said apophpytochrome

polypeptide is selected from the group consisting of a plant apophytochrome polypeptide, an algal apophytochrome polypeptide, and a cyanobacterial apophytochrome polypeptide; and a bilin, wherein the polypeptide is covalently linked to said bilin to form a florescent adduct. Claims 3 and 22 are drawn to the polypeptide consisting of about 390 amino acids. Claims 10 and 27 are drawn to the bilin being a tetrapyrrole. Claim 17 is drawn to a method of detecting the presence of a biomolecule in a sample, the method comprising: providing a sample comprising a biomolecule linked to a fluorescent adduct consisting of a bilin and an apophytochrome polypeptide of less than about 400 amino acids, which apophytochrome polypeptide comprises a lyase domain; contacting the sample with light which causes the fluorescent adduct to emit light; and detecting the emitted light, thereby detecting the presence of the biomolecule. Claim 18 is drawn to contacting the sample with light includes contacting the sample with light having a wavelength of about 570 nm. Claim 19 is drawn to detecting the emitted light includes detecting light having a wavelength of about 590 nm.

Hill et al., teach the expression of phytochrome apoprotein in *E.coli* and formation of photoactive chromoproteins by assembly with phycocyanobilin. Phytochromes contain covalently bound phytochromobilin chromobilin chromophores and the covalent linkage with tetrapyrrole (page 69, col. 2). Hill et al., also teach active chromopeptides of 59kDa, 45kDa and 39 kDa (page 69, col.2). Hill et la., teach phytochrome peptides having about 398 amino acids (page 69. col. 1). Hill et al., show detecting the emitted light a wavelengths of less than 600, 550 see figures 7, 8 and 9. Hill et la., teach sufficient formation procedures for recombinant apophytochromes with phycocyanobilin

or phytochromobilin for detection by absorption spectroscopy (page 74, col.1). Hill et al., teach the apoproteins were incubated with phycocyanobilin , irradiated with light which caused the emition of light and the spectra was then recorded (page 72, col.2).

Therefore Hill et al., teach the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 10-19 and 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clack et al., (Plant Mol. Bio. 1994. Vol. 25 :413-427) in view of Stryer et al., (US Patent 4,859,582).

Claim 1 is drawn to a composition comprising: an apophytochrome polypeptide consisting of less than about 400 amino acids, which apophytochrome polypeptide comprises a lyase domain having lyase activity, wherein said apophpytochrome polypeptide is selected from the group consisting of a plant apphytochrome polypeptide, an algal apophytochrome polypeptide, and a cyanobacterial apophytochrome polypeptide; and a bilin, wherein the polypeptide is covalently linked to said bilin to form a fluorescent adduct. Claims 10 and 27 are drawn to the bilin being a tetrapyrrole. Claim 11 and 28 are drawn to the bilin being phycoerythrobilin. Claim 12 is drawn to the fluorescent adduct being linked to a biomolecule. Claims 13 and 29 are drawn to the

biomolecule being selected from the group consisting of a protein, a carbohydrate, a lipid, and a nucleic acid. Claims 14 and 30 are drawn to the biomolecule being a nucleic acid. Claims 15 and 31 are drawn to the biomolecule being a protein. Claims 16 and 32 are drawn to the protein being an antibody.

Claim 17 is drawn to a method of detecting the presence of a biomolecule in a sample, the method comprising: providing a sample comprising a biomolecule linked to a fluorescent adduct consisting of a bilin and an apophytochrome polypeptide of less than about 400 amino acids, which apophytochrome polypeptide comprises a lyase domain, wherein the apophytochrome polypeptide is a plant apophytochrome polypeptide; contacting the sample with light which causes the fluorescent adduct to emit light; and detecting the emitted light, thereby detecting the presence of the biomolecule. Claim 18 is drawn to contacting the sample with light includes contacting the sample with light having a wavelength of about 570 nm. Claim 19 is drawn to detecting the emitted light includes detecting light having a wavelength of about 590 nm.

Clack et al., teach the sequence and expression of phytochrome apoproteins from the *Arabidopsis* plant. All of the detectable phytochrome apoprotein genes have been isolated and sequenced (page 414). Figures 3A and 3B show the derived amino acid sequence of the PHYD and PHYE genes. Figure 4 shows a plot of amino acid residues for five apoproteins, PHY A-E. The apoprotein of Clack et al., has 100% sequence identity to SEQ ID NO:9 and is a apophytochrome polypeptide consisting of less than 400 amino acids. Clack et al., teach products have 348 and 312 base pair, which are products having less than 400 amino acids. The phytochrome polypeptides

comprises regions important for chromophore attachment to the apoprotein (page 421, col. 1). Clack et al., also teach the amino and carboxy-terminal sequences important for biological activity (page 421, col.1). However Clack et al., do not teach a covalently linked bilin.

Stryer et al., teach fluorescent conjugates for analysis of molecules and cells. Stryer et al., teach composition comprising phycobiliproteins conjugated to a member of a specific binding pair (col. 2, lines 49-52). Stryer et al., teach biliproteins can be linked to any ligand of interest (col.3, lines 33-35). Stryer et al., teach that bilin proteins are easily conjugated covalently and there is ample literature for their conjugation (col. 2, lines 50-65 and col. 4, lines 25-28). The ligand can be any compound of interest including polypeptides, immunoglobulins or antibodies (col. 3, lines 38-68). For example, Stryer et al., teach phycobiliproteins have been studied and their fluorescent spectral properties are well known (col. 4-5, lines 68-2). Stryer et al., teach fluorescent probes are valuable reagents for analysis and separation of molecules in identification, determination and localization techniques (col. 1, lines 18-35). Stryer et al., biliproteins are readily conjugated and provide for high quantum efficiency with absorption and emission of long wavelengths in the visible and enhance the sensitivity and accuracy of methods involving ligand receptors reactions (col. 2, lines 20-25). Stryer et al., teach bilins are visible at wavelengths between 550nm and 650nm, see Table 1. Furthermore, the biliproteins can be used in immunoassays where the biliprotein serves as a fluorescent label and is conjugated to either a ligand or receptor for detection (col. 5-6,

lines 66-15). Example 9 teaches the sample with fluorescent adduct complex, and detecting a fluorescent signal at 576nm.

Therefore, it would have been prima facie obvious at the time of applicants' invention to modify the composition of Clack et al., which comprises a plant apophytochrome polypeptide consisting of less than about 400 amino acids, that comprises a lyase domain having lyase activity wherein the apoprotein is covalently linked to a bilin to form a fluorescent adduct as taught by Stryer et al., in order to provide fluorescent adducts for use in a wide variety of methods involving detection, analysis or measurement assays. One of ordinary skill in the art would have a reasonable expectation of success by including the bilin within the already fluorescent composition because are both known for their signaling ability and their unique spectral properties while Stryer et al., ease of covalent conjugation of the bilin and other molecules. Furthermore, no more than routine skill would have been required to covalently link the bilin to the apophytochrome polypeptide because Stryer et al., teach the ease of covalent conjugation. Finally it would have been prima facie obvious to combine the invention of Clack et al., and Stryer et al., to advantageously achieve fluorescent probes as valuable reagents for analysis and separation of molecules in identification, determination and localization techniques.

Claim Rejections - 35 USC § 103

8. Claims 1, 10-19 and 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marshall and Neale submitted to the EMBL Data Library March 1995 in view of in view of Stryer et al., (US Patent 4,859,582).

Claim 1 is drawn to a composition comprising: an apophytochrome polypeptide consisting of less than about 400 amino acids, which apophytochrome polypeptide comprises a lyase domain having lyase activity, wherein said apophpytochrome polypeptide is selected from the group consisting of a plant apophytochrome; and a bilin, wherein the polypeptide is covalently linked to said bilin to form a fluorescent adduct. Claims 10 and 27 are drawn to the bilin being a tetrapyrrole. Claim 11 and 28 are drawn to the bilin being phycoerythrobilin. Claim 12 is drawn to the fluorescent adduct being linked to a biomolecule. Claims 13 and 29 are drawn to the biomolecule being selected from the group consisting of a protein, a carbohydrate, a lipid, and a nucleic acid. Claims 14 and 30 are drawn to the biomolecule being a nucleic acid. Claims 15 and 31 are drawn to the biomolecule being a protein. Claims 16 and 32 are drawn to the protein being an antibody.

Claim 17 is drawn to a method of detecting the presence of a biomolecule in a sample, the method comprising: providing a sample comprising a biomolecule linked to a fluorescent adduct consisting of a bilin and an apophytochrome polypeptide of less than about 400 amino acids, which apophytochrome polypeptide comprises a lyase domain, wherein the apophytochrome polypeptide is a plant apophytochrome polypeptide; contacting the sample with light which causes the fluorescent adduct to

emit light; and detecting the emitted light, thereby detecting the presence of the biomolecule. Claim 18 is drawn to contacting the sample with light includes contacting the sample with light having a wavelength of about 570 nm. Claim 19 is drawn to detecting the emitted light includes detecting light having a wavelength of about 590 nm.

Marshall and Neale teach an apoprotein phytochrome fragment from Douglas Fir. The phytochromobilin of Marshall and Neale has 368 amino acids. Marshall and Neale teach a feature of the phytochromobilin has presence of the phytochromobilin covalent binding site. The phytochrome protein has accession number T09496 but was renamed Q40917.

However Marshall and Neale do not teach a covalently linked bilin and Stryer et al., has been discussed above.

Therefore, it would have been prima facie obvious at the time of applicants' invention to modify the composition of Marshall and Neale which comprises a plant apophytochrome polypeptide consisting of less than about 400 amino acids, that comprises a lyase domain having lyase activity wherein the apoprotein is covalently linked to a bilin to form a fluorescent adduct as taught by Stryer et al., in order to provide fluorescent adducts for use in a wide variety of methods involving detection, analysis or measurement assays. One of ordinary skill in the art would have a reasonable expectation of success by including the bilin within the already fluorescent composition because are both known for their signaling ability and their unique spectral properties while Stryer et al., ease of covalent conjugation of the bilin and other molecules. Furthermore, no more than routine skill would have been required to

covalently link the bilin to the apophytochrome polypeptide because Stryer et al., teach the ease of covalent conjugation. Finally it would have been prima facie obvious to combine the invention of Marshall and Neale and Stryer et al., to advantageously achieve fluorescent probes as valuable reagents for analysis and separation of molecules in identification, determination and localization techniques.

Conclusion

9. No claims allowed. It is noted that while claims 4-5, 7-8 and 23-26 are not rejected, the claims are objected to because the claims are dependant upon rejected claims.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/

Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645